ORIGINAL ARTICLES

URINARY TRACT INFECTIONS *
FROM A GENERAL PRACTICE STANDPOINT

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PART I

CHANGES in the treatment of urinary-tract infections have occurred with such rapidity during the past few years that urologists have found it difficult accurately to evaluate the various forms of therapy before they become obsolete. During this time the general practitioner has been literally swamped by the various drug houses with an apparently never-ending series of new urinary antiseptics; each one, not only claimed to be more efficient than its predecessor, but invariably proved to be more expensive.

The scope of the national advertising with which each of these new panaceas was launched invariably exceeded that of its predecessor, until the price of the product became so excessive as to arouse protest from both physician and patient. This was usually met with the assurance that their efficiency was in direct proportion to their cost: after all, first-class articles or services are usually expensive, and why should medicines prove any exception to that well-established rule? The possibility that a medicine might receive universal adoption on its merits alone seemed to occur to no one. It was taken for granted that a new urinary germicide, upon its presentation to the profession, would require as elaborate a build-up as that accorded the latest automobile model or movie star. That such a build-up might as frequently serve to hide the shortcomings of the product occurred to some of the more skeptical ones.

Such was the case when the efficacy as a urinary antiseptic of certain of the much-publicized azo dyes was demonstrated by the circulation of drawings and photographs of test-tubes and petre dishes. In the controlled test-tubes most of the noxious organisms commonly found in urine were seen to grow in great abundance, while in the culture media to which even minute amounts of the advertised dye were added growth was inhibited. Such an ocular proof of the antiseptic value of the product as that seemed beyond refutation; yet a graduate student named James Gillespie, presumably from Missouri, repeated the tests as described in the advertising matter, and in his thesis wrote: "Antisepsis in urine is quite different from antisepsis in water. Compounds which exert a striking bactericidal action in water may have this power greatly diminished or lost in urine. This well-recognized fact has excluded many drugs from the list of valuable urinary antiseptics. The value of every drug used for urinary antisepsis ought to be questioned until this antiseptic strength in urine can be experimentally demonstrated. Compounds, the antiseptic power of which is due to acid or basic properties, would become inert in the urine due to the buffer action of urinary salts. Other compounds containing silver become inert in the urine because silver is precipitated by the chlorids."

To demonstrate the correctness of these statements, he added a few drops of urine as well as the azo dyes to his culture media; and upon incubation the profusion of growth was as great in the tubes to which the dye had been added as in the controls. In the presence of urine, the much advertised germicidal action of these dyes for urinary infections was completely neutralized.

The beginning of this period of the active commercialization of urinary antiseptics dates roughly from the presentation of the first perfect germicide in the form of mercurochrome, which you will recall started as an intravenous drug, and after a rather colorful life has found its place as a popular substitute for iodin. The career of hexylresorcinol, alias capricol, has been similar. Starting as a urinary antiseptic par excellence at ten cents a capsule, it is now advertised as a tooth paste. It was during this period that the commercial laundries benefited, I believe, even more than our patients; for the amount of underwear that was stained by pyridium, serenium, and picrocain must have kept many an individual off the PWA rolls. In the meantime, that reliable friend of our early practice, urotropin, having changed its surname from hexamethynamin to methenamin had, like the aging wife, been abandoned and divorced while we philandered with these gayer and more colorful products. Like most such alliances, the younger consort proved fickle and inefficient, and we were then urged to become drug nihilists and combat our enemies in the urinary tract by diet, the ingestion of which, because of its high fat content, seemed impossible for any but an Eskimo, but which those in the temperate zone were expected to partake of for at least a fortnight if any lasting results were to be obtained. Yet the results of the ketogenic diet proved so illusory, except under the most rigid supervision, that it was soon abandoned, and the profession was assured that a similar but surer effect could be obtained by the administration of mandelic acid. Any of the profession who essays to take his own medicine in the form of the elixirs or syrups, in which form it is commonly dispensed, must agree that the ketogenic diet, difficult as it was to ingest, was preferable, and that the presence of a few pus cells and bacilli in the urine are much less disturbing to bodily comfort.

At the present time we are in the sulfanilamid stage. This drug seems destined to be the exception that proves the rule. It is cheap and, instead of being suddenly thrust upon us, we find that it has proved its usefulness gradually over a long period of time. Gelmo, working on the chemistry of azo dyes, was the first to mention this drug in 1908, while Dormack, director of the experimental pathologic laboratory of Elberfeld, Germany, was the first, in 1935, to point out its therapeutic possibilities.

SOME FUNDAMENTAL PRINCIPLES OF UROLOGIC PRACTICE

However, before discussing the efficacy of these various urinary antiseptics, it would seem pertinent to review briefly the diseases for which they are intended, and discuss some of the fundamental principles of urologic practice as they apply to infections of the urinary tract.

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Someone has said that the chief function of the urologist is to insure the adequate and constant drainage of the urinary tract. This is certainly a basic principle and, with very few exceptions, no method of therapy will long prove efficient if the passage of urine from the renal papellae to the urethral meatus is in any way obstructed. Probably nowhere is this so well clinically demonstrated as in the case of pyelitis of pregnancy. Here, for some reason, upon the exact cause of which the authorities differ, there occurs a dilatation of the upper urinary tract associated with urinary stasis. If infection is added, the clinical picture may become very grave. In the majority of cases such infection occurs on the right side, and the institution of ureteral catheter drainage will, in a few hours, by emptying the renal pelvis, return the highest of temperatures to normal with complete abatement of the most extreme degrees of prostration. In most cases drainage is all that is required. Without such urinary drainage all germicides are of little value although, administered in conjunction with drainage, they prove beneficial. We must consider, therefore, adequate drainage as imperative before any form of germicide can be expected to prove effective.

QUANTITY OF URINE OUTPUT

Certainly the next most important factor in all cases of urinary infection is the copious output of urine. If this is not possible by oral administration it should be given by subcutaneous or intravenous means either in the form of normal saline or five per cent glucose. In recent years the intravenous method has largely replaced the subcutaneous due, I think, to the fact that the subcutaneous method, when it first came into vogue, employed large needles resembling trocars, and the fluid was allowed to accumulate in considerable amounts in the subcutaneous tissues to the great discomfort of the patient. If the subcutaneous administration of fluids is given with multiple small needles, it may be run for days at a time with little discomfort and to great advantage. By this method, moreover, the possibility of embarrassing a faulty cardiac musculature is avoided, a risk that many believe to be associated with the intravenous method of administration. Certainly, any patient with an acute urinary infection should excrete in excess of 2,500 centimeters of urine daily; if the surrounding room temperature is high this will be difficult to obtain by oral administration. Furthermore, the ingestion of too great an amount of fluid by mouth upsets the gastro-intestinal tract, and the patient loses the benefits of adequate digestion and may develop so-called water intoxication, as described by Rowntree in his studies of the effect of pituitrin in cases of diabetes insipidus, with resultant serious pathologic changes in the nervous system.

Keyes has written that "the diagnosis of renal infection depends rather upon the arousing of the suspicions of the medical examiner to the fact that the patient may have a renal infection than upon anything else. Once renal infection is suspected, it can readily enough be diagnosed."

The reason for our neglect to more frequently recognized renal infection is due, I think, to the fact that we have come to associate pyuria with renal infection; the idea that one may exist without the other is seldom entertained, and yet clinical experience and painstaking study have demonstrated repeatedly that such may be the case. The fact that a carefully conducted physical examination frequently fails to indicate an involved kidney is also unquestionably responsible for our too frequent failure to have our suspicions aroused.

Although there are exceptions which, because of their rarity, may be disregarded, it is accurate to state that in the vast majority of cases renal infections occur either by the hematogenous or ascending route, and are apt to be associated with some form of urinary stasis either permanent or temporary.

RÔLE OF BACTERIA

A great variety of bacteria have been isolated, and reports vary as to the incidence of certain types. Thus, if the investigation includes many cases of pyelitis in children or during pregnancy, the incidence of Escherich's coli will be overwhelming; if such an investigation should be made in an institution like the Mayo Clinic, the colon organism will be far from the predominant one, though still in the majority.

Formerly it was customary, once having excluded the possibility of tuberculosis, to be satisfied with knowing merely if the infecting organism was a bacillus or a coccus. So rapidly has therapy progressed that today one can hardly be said to be carrying on the best type of attack unless he knows the organisms which he is attacking. At first this might seem to demand a bacteriological knowledge and equipment beyond the reach of most practitioners; but such is not the case, for urinary sediment stained by Gram's method generally proves sufficient, and only the more unusual types of bacteria need the assistance of a bacteriologist to correctly name them. In fact, the stained sediment is not infrequently more accurate than cultures, especially in the case of renal infections, as is shown by a recent study of Buchtel.

That bacteria can reach the kidney by the blood stream is self-evident, but fortunately few survive long enough to make the journey, and of those that do, the endothelial surfaces of the kidney tissues serve rapidly to annihilate the vast majority. The best clinical example of this is probably the so-called urethral chill following instrumentation, with a rapid rise of temperature to extreme heights associated with prostration of the patient, to be followed the next day by his discharge from the hospital apparently in the best of health. More frequent cases of hematogenous infection are those of the coccal type, which come from boils and carbuncles and which, either because of their increased virulence or repeated attacks, manage to become established in the renal parenchyma, and not infrequently lead to perinephritic abscess or carbuncle of the kidney. Closely associated with this group are the cases of coccal infection arriving from the upper respiratory tract during the course of acute respiratory infection. In these cases the urine excretion fails to show any pyuria, but if during the early course of the infection the urine specimen is

centrifuged for a prolonged period of time and carefully stained, the presence of cocci will be demonstrable. Their presence will explain the fever and elevated pulse, which are usually out of proportion to the severity of the respiratory involvement. In such cases a careful physical examination will generally elicit a point of tenderness to palpation at the costomuscular angle, a finding which will leave the diagnosis beyond question. There are few conditions in which it is so difficult to correlate the clinical picture, the urinary findings, and the pathological conditions. The pathologist seldom sees kidneys of this type, for, fortunately, the condition is rarely fatal; and if it is, the pathologic changes have progressed far beyond those that were present at the onset of the condition. However, the numerous renal scars seen in the routine examination of autopsy materially attest to the accuracy of our clinical deductions.

Because the infection is principally in the cortex of the kidney, the urine does not contain any cellular elements, and investigation by intravenous urography will usually prove negative, as the infection does not produce abnormalities discoverable by these methods. Of considerable clinical importance is the regular early development of perinephritis, which produces the tenderness so characteristically found in the costomuscular angle.

With this group must be included the cases of pyelonephritis which are the result of focal infection. While the relationship between an abscessed tooth, infected tonsil, cervix or prostate is not as easily demonstrated either clinically or experimentally, the best opinion today seems to favor such a relationship. It may be possible as our knowledge advances we shall discover that these distant foci, instead of supplying the actual organisms that infect the kidney, produce a toxin which, by its chemical affinity for renal tissues, makes possible the continued growth of the infection either by neutralizing the natural immune processes, or so affecting the involved tissue as to make the site favorable for growth. Certainly, a careful review of experimental work along this line points in that direction.

(To be continued)

TISSUE CHANGES IN CHRONIC INTOXICATION OF BARBITALS*

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TISSUE changes have been reported several times in patients following acute fatal poisoning by barbital and its derivatives,[1-10] the main pathological changes being in the central nervous system, liver, kidneys, and skin. Somewhat similar changes have also been reported in experimental animals.[11-15] However, no one thus far has reproduced, experimentally, the dermatitis observed clinically in sensitive individuals using these compounds. In connection with another study, it was observed in this laboratory that dogs anesthetized repeatedly with pentobarbital developed a macular papular exanthem, accompanied by depilation, cracking and oozing, and resembling the clinical picture of barbital dermatitis. In the hope that this phenomenon might be reproduced which would permit an experimental study of the clinical manifestations of barbital idiosyncrasy, the following experiments were performed to study the phenomenon in more detail. In brief, there were carried out long-continued administrations to dogs and white rats of various members of the barbital group and histological examinations for possible alterations in skin and other organs.

PENTOBARBITAL AND AMYTAL IN DOGS

Pentobarbital.

Fifteen young adult dogs, fourteen males and one female, were used, three of the males serving as controls. The animals were fed a diet of commercially prepared dog food and water, and kept in the regular animal quarters. Food was withdrawn twice weekly for eighteen to twenty-four hours, then an intraperitoneal injection was given of pentobarbital† (sodium ethyl (methyl-propyl carbinyl) barbiturate), 50 milligrams per kilogram body weight, dissolved in three cubic centimeters of distilled water. Narcosis resulted in from thirty seconds to ten minutes and lasted from ten to twelve hours.

Four dogs died of intestinal perforation and peritonitis, following injection. Histologic examination of these animals showed cloudy swelling of the liver, kidney, spleen, and heart muscle, with septic infarcts and areas of necrosis in which bacilli were present. It is doubtful if these changes had any relationship to the effects of the drug. The remaining seven males developed patchy areas of depilation, and a macular papular erythematous exanthem of the entire body except the head, neck and saddle, in an average time of fifty days.

When the skin rashes appeared, an attempt was made to determine in each dog whether a specific dermal sensitivity was present which could be demonstrated by patch tests. Accordingly, the hair was shaved from the dorsolateral thorax bilaterally over an area 10 by 10 centimeters. Gauze squares, 3 by 3 centimeters, were saturated with solutions and applied to the shaved areas for twenty-four hours as follows: (1) pentobarbital in distilled water; (2) dog urine, obtained by catheterization of the bladder one hour after narcosis developed; and (3) distilled water. However, the patch tests were all negative in all the animals in the thirteen tests made.

The female dog developed ataxia of the hind legs after fifty days, and by the fifty-fifth day was completely ataxic, and had urinary incontinence. Sensation was normal as far as could be determined. However, these signs completely disappeared after the one-hundredth day. This animal became pregnant during the course of the experiment and gave birth to six pups. These were sacrificed when they were two weeks old; histologic examination of the skin and vital organs showed them to be normal.

Injections were continued over a period of two hundred days, during which time about sixty in-

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† Supplied by Abbott Laboratories.